## MITIGATION - SCIENCE AND TECHNOLOGY ADVANCES FOR CHEMICAL AND BIOLOGICAL HAZARD MITIGATION

# Comparing Immune Responses To B. Pseudomallei Infection In A Lymphoid Follicle MPS and a C57BL/6 Mouse Model

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Microphysiological systems (MPS) offer several advantages when compared to conventional methods of infectious disease modeling; such advantages include reproduction of complex human tissue microenvironments not possible in 2D cell culture, and lower operation costs than those associated with animal models. As such, MPS optimization, characterization, and demonstration of their ability to accurately reproduce in vivo infection dynamics are of immediate importance.

Burkholderia pseudomallei, a select agent pathogen, is particularly virulent due to the bacteria's ability to undermine and evade the host immune system, using strategies such as multinucleated giant cell (MNGC) formation and C3b evasion. Unfortunately, this commonly leads to delayed or incorrect diagnoses, with the accompanying delay of effective antibiotic treatment. Delayed diagnosis of B. pseudomallei infection further exacerbates treatment difficulties by allowing infection to progress into disseminated and/or chronic forms. Untreated B. pseudomallei infections have mortality rates approaching 40%, but even with proper treatment, mortality rates approach 20%. Broadly speaking, identification of relevant biomarkers of infection can serve several functions such as improving diagnostics and guiding selection of appropriate treatments. Identifying indicators of early Burkholderia infection would be a useful resource for improving prognoses by informing treatment options before disseminated and/or chronic infection sets in.

In this work, we compare immune responses to B. pseudomallei exposure in a C57BL/6 mouse model and lymphoid follicle MPS. The lymphoid follicle MPS was chosen over other MPS models because of B. pseudomallei's known interactions with the host immune system. Lymphoid follicle MPS are produced using primary human peripheral blood mononuclear cells (PBMCs) dispersed through an artificial matrix, which is seeded onto microfluidics chips. This immune system based MPS is more physiologically relevant than typical 2D macrophage cell cultures, as it contains actual ratios of the various white blood cells found in human blood and simulates the shear stress to which B. pseudomallei is exposed in vivo.

Using targeted transcriptomics, we assessed the inflammatory response to B. pseudomallei in whole mouse blood, as measured by differentially regulated genes (DEGs) known to participate in an immune response. We found three genes to be significantly upregulated in the blood: LCN2, GBP2, and CXCL10, which are affiliated with activated astrocytes, management of intracellular infection, and T cell recruitment, respectively. We will perform the same targeted transcriptomics analysis on RNA extracted from lymphoid follicle MPS samples and cross-reference the results to determine the degree of similarity in the inflammatory responses between these two models. The information gathered from this study will provide a robust baseline for further examination of lymphoid follicle MPS systems and their utility in providing physiologically relevant immune responses to infectious agent.